REMARKS

The election with traverse of Group II (claims 3 - 8, 2 - 15, 17 and 18) and the species of Formula I has been acknowledged. The restriction requirement is made final. Claims 3 - 7, 9 - 15, 17 - 26 and 36 - 40 are pending and were examined. Claims 7 and 24 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite and failing to particularly point out and distinctly claim the subject matter that the applicants regard as the invention. Claims 3 - 7, 9 - 15, 17 - 26 and 35 - 40 under 35 U.S.C. § 112, first paragraph for allegedly lacking written description and enablement. Claims 3 - 7, 9 - 15, 18 - 22, 24 - 26 and 36 - 40 are rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by Huille *et al.*, (WO 00/30618, June 2, 2000), as evidenced by the Handbook of Chemistry and Physics, 88th Ed. 2008 and Akiyoshi *et al.*, J. Controlled Release, 1998; 54:313 - 320. claims 3 - 7, 9 - 15, 17 - 26 and 36 - 40 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Huille *et al.*, (the '171 patent), Lambert *et al.*, (U.S. Patent No. 7,030,155) and Singh *et al.*, (U.S. Patent No. 5,102,872) as evidenced by the Handbook of Chemistry and Physics, 88th Ed. 2008 and Akiyoshi *et al.*, J. Controlled Release, 1998; 54:313 - 320. Reconsideration in view of the following remarks is respectfully requested.

Rejection of claims under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 7 and 24 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite and failing to particularly point out and distinctly claim the subject matter that the applicants regard as the invention. Office Action at pages 4 - 5. The Examiner alleges that claim 7 is indefinite because it sets forth that the organic cations may be based upon polyamine and the claim also sets forth polyethylenimine as an alternative organic cation, which

the Examiner alleges is a narrower range than polyamine. The Examiner is mistaken and confused as to the chemical identities of these two compounds. One of skill in the art would understand that a polyamine is an organic compound having two or more primary amine groups, whereas polyethylenimine contains either secondary amines, or a mixture of primary, secondary and tertiary amines. Rather than being a narrower range of the polyamine, polyethlenimine is a separate chemical entity and is an alternative organic cation to polyamine set forth in claim 7 as part of a Markush group. Also, claim 7 properly sets forth the alternatives as a proper Markush group (see, MPEP 803.02) and does not use the "such as" language relied upon in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989). Because one of skill in the art would understand the polyamine and polyethylenimine to be separate chemical entities, rather than a broad and narrow range, and claim 7 is a proper Markush group type claim, the applicants respectfully request that the Examiner withdraw the rejection of claim 7 as being indefinite under 35 U.S.C. § 112, second paragraph.

Likewise, claim 24 sets forth a Markush group of alternative active principles, not a broad and narrow range. Again, the Examiner is mistaken and confused as to the claiming of elements in a Markush group compared to claiming a broad and narrow range in the same claim. Claim 24 does not set forth a broad range followed by the language "such as" and then set forth a narrow range, which was the relevant language in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), and upon which the Examiner relies to allege that claim 24 is indefinite. Claim 24 clearly sets forth that the active principle can be "selected from the group consisting of . . . and . . ." This is the proper language to claim alternatives as a Markush group. See, MPEP 803.02. The applicants, therefore, respectfully request that the Examiner withdraw the rejection of claim 24 as being indefinite under 35 U.S.C. § 112, second paragraph.

Rejection of claims under 35 U.S.C. § 112, first paragraph-enablement

The Examiner rejects claims 3 - 7, 9 - 15, 17 - 26 and 35 - 40 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable one of skill in the art to make or use the invention commensurate in scope with the claims. Office Action at page 5. Specifically, the Examiner alleges that the specification does not reasonably provide enablement for the genus of structural variants comprising at least one active principle, a biodegradable polymer with hydrophobic groups, or the polymers of Formula I. *Id.* at page 5. The Examiner alleges that the specification discloses an IL - 2 formulation comprising polyglutamate grafted with α-tocopherol, but no other representative structures of Formula I, or structures of a biodegradable polymer and an active principle are adequately taught in the specification. *Id.* at page 8.

As a matter of Patent Office practice, the burden rests upon the Patent Office to establish a *prima facie* case of a failure to comply with 35 U.S.C. ¶ 112, first paragraph, with respect to the invention described and claimed in applicants' presumptively enabling patent application. *In re Marzocchi*, 58 C.C.P.A. 1069,439 F.2d 220, 169 USPQ 367 (C.C.P.A. 1971). The legal standard for enablement is whether one reasonably skilled in the art could make and use the invention based on the disclosure of the application and knowledge in the art without undue experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly excessive." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is

permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) (quotation and citation omitted). In *Johns Hopkins Univ. v. CellPro*, 152 F.3d 1342 (C.A.Fed. (Del.) 1998), the Court of Appeals for the Federal Circuit rejected appellants' argument that methods for producing CD24 antibodies were generally "more difficult" than other monoclonal antibodies as sufficient to show lack of enablement. Here, the specification provides enablement to one of skill in the art to make and use the claimed invention commensurate in scope with the claims.

The specification discloses examples of polymers with different hydrophobic groups, including cholesterol and n - dodecanol. Specification at Example 2, page 26. Furthermore, Example 5, describes an example of another protein associating with a polymer encompassed by the present invention and Example 6 provides details of the gelling concentration of IL - 2 formulations associated with various polymers, including a polymer containing n - dodecanol as the hydrophobic group. *Id.* at Examples 5 & 6, pages 28 - 29. Moreover, the specification discloses that the state of the art was such that various polymers with various active principles were known and therefore, one of skill in the art would know and understand how to manufacture different polymers and how to associate active principles with these polymers. *See, Id.* at pages 3 - 7.

Additionally, given this basic understanding of chemical synthesis by one of ordinary skill in the art, the specification discloses sufficient detail that any experimentation would not be undue, but merely routine. The specification discloses the properties of the polymers and

formulations of the claimed invention and tests to determine if the polymers and formulations have these properties. *See, Id.* at pages 9 - 19. One of skill in the art, therefore, would be able to manufacture a range of formulations and given the teachings of the specification, it would be routine experimentation to determine if the manufactured formulation was within the scope of the claimed invention. Accordingly, the applicants respectfully request the Examiner withdraw the rejection of claims 3 - 7, 9 - 15, 17 - 26 and 35 - 40 under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement.

Rejection of claims under 35 U.S.C. § 112, first paragraph – written description

The Examiner rejects claims 3 - 7, 9 - 15, 17 - 26 and 35 - 40 under 35 U.S.C. § 112, first paragraph, alleging that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, the Examiner alleges that because there is insufficient recitation of distinguishing characteristics, the specification does not provide adequate written description for a liquid formulation comprising at least one active principle, which is an interleukin, and a biodegradable polymer with hydrophobic groups. Office Action at page 11.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112,¶ 1 "Written Description" Requirement (herein after the "Guidelines") state that "[to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." 66 Fed. Reg. 1099, 1104 (2001). This requirement for claims directed to a genus can be satisfied by a sufficient description of a representative number

of species by actual reduction to practice and that the "representative number of species" means, that the species are representative of the entire genus. *Id.* at 1106. What constitutes a "'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." *Id.* at 1106. In some cases, disclosure of one species will be sufficient. *Id.* at 1106. Possession of the invention can be shown in any one of several ways, including by a description of physical properties in combination with a description of functional characteristics. *Id.* at 1106.

The specification discloses the chemical structure of polymers encompassed by the claimed invention and the physical properties and functional characteristics of the polymers. *See*, Specification at pages 15 - 19. Further, the specification discloses that the polymers encompassed by the claimed invention can associate spontaneously with active principles such as proteins, peptides and small molecules (*see*, page 19) and lists the possible active principles. See page 23. Moreover, the specification discloses examples of polymers with different hydrophobic groups and associated with different active principles. *See, Id.* at Example 2, page 26 and Examples 5 & 6, pages 28 - 29. The description in the specification of the chemical structure, physical properties and functional characteristics of the polymers and formulations encompassed by the claimed invention, coupled with the disclosure of representative examples of the claimed invention necessarily mean that one of ordinary skill in the art would appreciate and understand that the applicants were in possession of the common attributes of the elements possessed by the members of the genus in view of the species disclosed. Accordingly, the applicants respectfully request that the Examiner withdraw the rejection of claims 3 - 7, 9 - 15,

17 - 26 and 35 - 40 under 35 U.S.C. § 112, first paragraph for allegedly lacking written description.

Rejection of claims under 35 U.S.C. § 102

Claims 3 - 7, 9 - 15, 18 - 22, 24 - 26 and 36 - 40 are rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by Huille *et al.*, (WO 00/30618, June 2, 2000) ("Huille"), as evidenced by the Handbook of Chemistry and Physics, 88th Ed. 2008 and Akiyoshi *et al.*, J. Controlled Release, 1998; 54:313 – 320 ("Akioyshi"). Specifically, the Examiner alleges that absent evidence to the contrary, the 0.5% bovine albumin solution taught in the Huille publication (Example 7 of U.S. Patent No. 6,630,171, ("the '171 patent") which the Examiner alleges is the U.S. version of the publication), would permit the spontaneous dissociation reaction of releasing the active principal on a concentration dependent basis. Office Action at page 13.

In order for a claim to be anticipated under 35 U.S.C. § 102, the reference must teach every element of the claim. Furthermore, "the identical invention must be shown in as complete detail as is contained in the . . . claim." *See* MPEP 2131, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir 1987). See MPEP 2131.01. "To establish inherency, . . . the missing descriptive matter must be necessarily present in the thing described in the reference, . . . and be so recognized by persons of ordinary skill." *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950 - 51 (Fed. Cir. 1999). The fact that a certain characteristic may occur or be

present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

One of ordinary skill in the art would understand that a 0.5% solution of bovine albumin is equivalent to 0.5g of bovine albumin per 100 ml, which equates to 5 mg/ml. Claim 3, however, sets forth that the aqueous solution comprises bovine serum albumin at a concentration of 30 mg/ml. Additionally, claim 3 sets forth that a gelled deposit forms in vitro at this concentration of bovine serum albumin. As noted above, to anticipate a claim, each and every element must be found either expressly or inherently in a single prior art reference. The Huille publication (nor the '171 patent) does not disclose a bovine serum albumin concentration of 30 mg/ml and does not disclose a gelled deposit formed in a solution of 5 mg/ml of bovine albumin. Also, as noted above, to establish inherency the missing element must be necessarily present and be recognized as such by one of skill in the art. Huille (the '171 patent) is missing a concentration of 30 mg/ml of bovine albumin. A solution of 0.5% bovine albumin (5 mg/ml) does not necessarily mean that 30 mg/ml is present and one of ordinary skill in the art would certainly not recognize that 30 mg/ml must be present when 5 mg/ml is present. Furthermore, there is no express disclosure of a gelled deposit in Huille (the '171 patent) and one of ordinary skill in the art would certainly not recognize that a solution of 5 mg/ml of bovine albumin would necessarily mean that a gelled deposit would be present. Accordingly, one of skill in the art would understand that not all the elements of the claimed invention are present in the Huille (the '171 patent).

Additionally, the Examiner alleges that the viscosity of water meets the limitations of claims 3, 5 and 20. Office Action at page 13. The applicants are confused as to the Examiner's assertion because the applicants are not claiming the "invention" of water. The claims are

directed to liquid formulations of polymers and active principles. Water would not contain the presently claimed polymers and active principles. The other claims the Examiner alleges are anticipated by Huille (the '171 patent) depend directly or indirectly from claim 3 and therefore, contain all the elements of claim 3. Thus, the claims are not anticipated by Huille (the '171 patent) because it does not disclose all the elements, either expressly or inherently. Accordingly, the applicants respectfully request that the Examiner withdraw the rejection of claims 3 - 7, 9 - 15, 18 - 22, 24 - 26 and 36 - 40 under 35 U.S.C. § 102(b).

Rejection of claims under 35 U.S.C. § 103

The Examiner rejects claims 3 - 7, 9 - 15, 17 - 26 and 36 - 40 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Huille (the '171 patent), Lambert *et al.*, (U.S. Patent No. 7,030,155) ("Lambert") and Singh *et al.*, (U.S. Patent No. 5,102,872) ("Singh") as evidenced by the Handbook of Chemistry and Physics, 88th Ed. 2008 and Akiyoshi. Office Action at pages 15 - 17. The Examiner sets forth several arguments that the claimed invention is obvious in view of the cited references that rely primarily on the argument proposed under the rejection based on 35 U.S.C. § 102(b) in relation to the teachings of Huille (the '171 patent). Initially the applicants note that this rejection of the claimed invention under 35 U.S.C. § 103(a) based upon the combination of Huille, Lambert, and Singh, is acknowledgement by the Examiner that Huille is not an anticipatory reference under 35 U.S.C. § 102(b), because the additional references were required by the Examiner to provide elements missing from Huille (the '171 patent). The applicants reiterate their request that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 102(b).

The burden is on the Examiner to make a *prima facie* case of obviousness, which requires an objective analysis as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). In *KSR International v. Teleflex Inc.*, 127 S.Ct 1727, 82 USPQ2d 1385 (2007), the Court affirmed that this analysis includes the following factual inquiries: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art. The Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* state that, having undertaken the factual inquiries of *Graham*, a rejection under 35 U.S.C. § 103 may be supported by one or more of the following rationales: (1) combining prior art elements according to known methods to yield predictable results; (2) simple substitution of one known element for another to obtain predictable results; (3) use of a known technique to improve similar devices in the same way; (4) applying a known technique to a known device ready for improvement to yield predictable results; (5) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (6) variations that would have been predictable to one of ordinary skill in the art; and (7) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention. 72 Fed. Reg. 57526, at 57529 (October 10, 2007). Each of the above - noted rationales require predictability in the art and/or a reasonable expectation of success, and the Examiner must consider objective evidence which rebuts such predictability and reasonable expectation of success. This objective evidence or secondary considerations may include unexpected results and/or failure of others (*e.g.*, evidence teaching away from the currently claimed invention), evidence of commercial success, and long - felt but unsolved

needs, as found in the specification as - filed or other source. *Id.* When considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1740, 82 USPQ2d at 1396. Here, the Examiner has not met this burden.

Scope and content of the prior art

Huille (the '171 patent) discloses delivery particles based upon linear amphiphillic polyamino acids with α - peptide chains, for active principals, where in the delivery particles are spontaneously formed in water and are capable of combining with the active principal and releasing the active principal in a prolonged and controlled manner in vivo. *See,* the '171 patent at Abstract.

Lambert is directed to pharmaceutical compositions containing tocopherol, with and without an aqueous phase, a surfactant and a therapeutic agent. Lambert at col. 4, ll. 55 - 59. The tocopherol acts as a carrier for therapeutic drugs and can be used as a hydrophobic dispersed phase of emulsions, a self emulsifying system, microemulsions or a PEGylated tocopherol. *Id.* at col. 12, l. 56 - col. 13, l. 45.

Singh is directed to methods of controlling shipping fever or other adverse reactions in livestock by administration of IL - 2 and formulations of IL - 2 for controlled release. Singh at col. 4, ll. 19 - 35. Singh *et al.*, disclose formulations of PEGylated IL - 2 and human serum albumin (HSA) in a ratio of about 1:5 to about 1:30 by weight. *Id.* at col. 6, ll. 2 - 5 and col. 13, ll. 45 - 60.

Differences between the claimed invention and the prior art

As noted above, in relation to the rejection under 35 U.S.C. § 102(b), Huille (the '171 patent) does not disclose expressly, or inherently, a gelled deposit or a solution containing 30 mg/ml of bovine serum albumin. The combination of Huille (the '171 patent), Lambert, and Singh does not cure this deficiency. The combination of references cited by the Examiner, therefore, does not disclose every element of the claimed invention.

Resolving the level of ordinary skill in the pertinent art

One of ordinary skill in the pertinent art would have a Ph.D. in molecular biology, biochemistry or a related discipline and have several years post doctoral experience in molecular biology, biochemistry or a related discipline. The Examiner, however, does not address the level of ordinary skill in the art, despite recognizing it as one of the Graham factors. Office Action at page 14. The Examiner does, however, determine that the relevant field would be molecular biology. Office Action at page 15. Without a determination of the level of ordinary skill in the pertinent art it is difficult, if not impossible, for the Examiner to ascertain what one of ordinary skill in the art would understand from the combined teachings of the alleged prior art. The differences between the scope and content of the prior art and the claimed invention are such that one of ordinary skill in the pertinent art would not understand the claimed invention to be obvious in view of the combination set forth by the Examiner.

Having ascertained the Graham factors for obviousness, a rejection under 35 U.S.C. § 103 may be supported by one or more of the following rationales: (1) combining prior art elements according to known methods to yield predictable results; (2) simple substitution of one known element for another to obtain predictable results; (3) use of a known technique to

improve similar devices in the same way; (4) applying a known technique to a known device ready for improvement to yield predictable results; (5) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (6) variations that would have been predictable to one of ordinary skill in the art; and (7) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention.

The Examiner has not set forth any support under any of these rationales for the rejection under 35 U.S.C. § 103 and the applicants have demonstrated that this further analysis is unnecessary as the combination cited by the Examiner does not disclose all the elements of the claimed invention. Accordingly, the applicants respectfully request the Examiner withdraw the rejection of claims 3 - 7, 9 - 15, 17 - 26 and 36 - 40 under 35 U.S.C. § 103(a) for allegedly being obvious in view of the prior art.

Obviousness - type Double Patenting Rejections

The Examiner rejects the currently pending claims under the doctrine of obviousness - type double patenting, alleging that the claims are not patentably distinct from claims in issued patents and co - pending applications that have a common assignee with the present application. The applicants note these rejections and shall consider filing terminal disclaimers when the Examiner indicates allowable subject matter in the instant application.

Conclusion

In view of the foregoing amendments and remarks, the applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Applicants submit concurrently a request for a one-month extension of time under 37 C.F.R. 1.136 and the accompanying fee. Please charge our Credit Card in the amount of $130.00 covering the fee set forth in 37 CFR 1.136(a). In the event that any additional extension of time is necessary to prevent the abandonment of this patent application, then such extension of time is petitioned. The U.S. Patent and Trademark Office is authorized to charge any additional fees that may be required in conjunction with this submission to Deposit Account Number 50-2228, referencing matter number 022290.0158PTUS, from which the undersigned is authorized to draw.

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Respectfully submitted,

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